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Neurological disorders in Gulf War veterans

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We present a review of neurological function in Gulf War veterans (GWV). Twenty-two studies were reviewed, including large hospitalization and registry studies, large population-based epidemiological studies, investigations of a single military unit, small uncontrolled studies of ill veterans and small controlled studies of veterans. In nearly all studies, neurological function was normal in most GWVs, except for a small proportion who were diagnosed with compression neuropathies (carpal tunnel syndrome or ulnar neuropathy). In the great majority of controlled studies, there were no differences in the rates of neurological abnormalities in GWVs and controls. In a national US study, the incidence of amyotrophic lateral sclerosis (ALS) seems to be significantly increased in GWVs, compared to the rate in controls. However, it is possible that military service, in general, might be associated with an increased risk of ALS, rather than Gulf War service in particular. Taken together, the conclusion is that if a neurological examination in a GWV is within normal limits, then extensive neurological testing is unlikely to diagnose occult neurological disorders.

Keywords: Gulf War; veteran; neuromuscular; neuropathy; amyotrophic lateral sclerosis; motor neuron disease

1. INTRODUCTION

Gulf War veterans (GWVs) have reported an increase in symptoms that could be due to central or peripheral nervous system (PNS) disorders, compared to non-deployed veterans. The five most frequently reported symptoms in the Department of Defense (DoD) Gulf War Registry were: muscle (and joint) pain (52%), fatigue (47%), headache (41%), memory problems (36%) and sleep disturbances (36%) (VA & DoD 2002). Other studies have reported memory and concentration problems, sleep disturbances, muscle pain and weakness, sensory disturbance of the limbs (such as tingling and numbness) and muscle cramps (Davis *et al*. 2004). Some of these symptoms could also be related to psychiatric conditions, such as major depression, posttraumatic stress disorder (PTSD) or anxiety disorders. Two other reviews, in this journal, focus on the findings of neuropsychological, neuroimaging and psychiatric evaluations in GWVs, which could be relevant to such symptoms (see Gifford *et al*. 2006; Vasterling & Bremner 2006).

Despite the many studies in GWVs, two questions remain controversial: (i) Is there a neurological illness that is specific to GWVs? (ii) Is there any Gulf War-related increase in known neurological diseases? These questions continue to generate strong opinions on both sides (Couzin 2004; Deahl 2005).

In this paper, we undertook a comprehensive review of all the published studies investigating the neurological basis for Gulf War-related symptoms. In conducting this review, we considered the following four questions:

(i) What are the prevalence and the range of neurological type symptoms?
(ii) Do the neurological type symptoms cluster in a way that might suggest specific neurological disorders?
(iii) Are the neurological symptoms reported by GWVs associated with any objective neurological abnormality; and if so, do these neurological abnormalities suggest any pattern of known neurological disease or specific neurological system impairment?
(iv) Is there evidence for an increased incidence of any neurological disease in GWVs?

2. METHODS

We identified relevant studies for this review by searching MEDLINE with the keywords Gulf War, Persian Gulf War, Desert Storm, Desert Shield, Gulf War illness(es), Gulf War syndrome, Persian Gulf syndrome, GWV and Gulf veteran between August 1990 and October 2005. We reviewed the bibliographies of the identified studies to find any additional relevant studies. We also screened the bibliographies of reports by expert panels of the Institute of Medicine and the publication lists contained in the US federal government *Annual Reports to Congress* on the research portfolio on GWVs from 1996 to 2003 (the most recent report; Deployment Health Working Group Research Subcommittee 2005).

Studies were included in the review if they reported the findings of neurological examinations or neurophysiology testing in GWVs. We excluded studies that were not published in English or those that were focused on neurological symptoms alone, without any objective

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One contribution of 17 to a Theme Issue 'The health of Gulf War veterans'.

evaluations. Studies that focused on neuropsychological testing or on neuroimaging were also excluded, since they are reviewed in another paper in this journal (Vasterling & Bremner 2006).

3. OVERVIEW OF THE STUDIES RELEVANT TO NEUROLOGICAL FUNCTION

A total of 22 studies were included in this review, with some studies resulting in more than one publication. These included large hospitalization and registry studies, large population-based epidemiological studies, cluster investigations that focused on a single military unit, small uncontrolled studies of ill veterans, and small controlled studies of veterans. A total of 11 studies have detailed the findings of neurological examinations in GWVs. These 11 studies are listed in the first three paragraphs below and their methods and results are summarized in table 1.

Four population-based epidemiological studies of neurological function have been performed: two in the US, one in the UK and one in Australia (Ismail *et al.* 1999; McCauley *et al.* 1999; Unwin *et al.* 1999; Kang *et al.* 2000; Bourdette *et al.* 2001; McCauley *et al.* 2002; Sharief *et al.* 2002; Davis *et al.* 2004; Rose *et al.* 2004; Eisen *et al.* 2005; Kelsall *et al.* 2005).

Two cluster investigations focused on particular military units that were chosen for evaluation, since their members reported a high prevalence of disabling symptoms. One study included 158 service personnel out of the 490 members of the Pennsylvania 193rd Air Force National Guard unit who deployed to the Gulf War (Centers for Disease Control and Prevention (CDC) 1995; IOM 1996; Fukuda *et al.* 1998). The other study included 249 members of 606 GWVs, who were part of the 24th Naval Mobile Construction Battalion, a reserve battalion that was located in five southeastern US states (Institute of Medicine 1995; Haley *et al.* 1997*a*,*b*; Roland *et al.* 2000; Haley *et al.* 2004).

Four uncontrolled studies focused on small samples of treatment-seeking veterans: 65 ill GWVs in Seattle (Newmark & Clayton 1995); 20 ill GWVs in San Antonio (Amato *et al.* 1997); 12 ill GWVs in San Juan, Puerto Rico (Rivera-Zayas *et al.* 2001); and 33 ill GWVs in London (Lee *et al.* 2005). A fifth small study included 14 ill GWVs and 13 healthy, non-military controls in Glasgow, Scotland (Jamal *et al.* 1996).

Three population-based studies of hospitalizations have been published (Gray *et al.* 2000; Smith *et al.* 2004*a*,*b*). Three studies based on the DoD and VA Gulf War Registry programs and the UK Medical Assessment Programme have been published (Joseph & the Comprehensive Clinical Evaluation Program Evaluation Team 1997; VA & DoD 2002; Bale & Lee 2005).

Three studies focused on neurophysiology testing, which did not include neurological examinations (Peckerman *et al.* 2000, 2003; Joseph *et al.* 2004; Stein *et al.* 2004).

Two studies focused on the incidence of amyotrophic lateral sclerosis (ALS; motor neuron disease) in GWVs (Haley 2003; Horner *et al.* 2003).

Some of the initial investigations resulted in populations of GWVs of particular interest who underwent additional evaluations. For example, the epidemiological studies in the UK published in 1999 yielded data on the rates and types of various symptoms (Unwin *et al.* 1999). Further studies of selected subjects from this survey focused on neurophysiological investigations and muscle function (Sharief *et al.* 2002; Rose *et al.* 2004). Similar approaches were taken in other population-based epidemiological studies and in the cluster studies of veterans belonging to specific military units.

Each study is described under the first question that it addresses. However, the findings of some studies address more than one question, so their findings are placed under two or more questions, as appropriate.

4. WHAT ARE THE PREVALENCE AND THE RANGE OF NEUROLOGICAL TYPE SYMPTOMS?

This question is best answered by reviewing hospitalization data, registry data and population-based data. Although the Gulf War registry programs were not designed as research studies, clinical data from these programs are relevant, because these programs include thousands of GWVs with health concerns who received systematic and thorough medical evaluations. Hospitalization data and registry data are biased towards the more severely affected subjects; nonetheless, these data provide considerable insight into the relative frequency of neurological disorders.

(a) *Hospitalization data on neurological disorders*

Three population-based studies of hospitalizations have been published, as well as three large studies based on the DoD and VA Gulf War Registry programs and the UK Medical Assessment Programme (Joseph & the Comprehensive Clinical Evaluation Program Evaluation Team 1997; Gray *et al.* 2000; VA & DoD 2002; Smith *et al.* 2004*a*,*b*; Bale & Lee 2005).

The types and rates of hospitalizations during the Gulf War have been evaluated, focusing on US service members who were hospitalized within the Kuwait theatre of operations or who were medically evacuated to DoD treatment facilities in Europe (Smith *et al.* 2004*a*). This study included 683 479 US service personnel who were deployed during the period from 1 August 1990 to 31 July 1991 (98% of the total of 697 000 deployed US troops). The study population was 93% male, 67% white and 56% were age 26 or younger. 18 631 individuals were hospitalized (2.7% of 683 479 personnel), with a total of 30 740 diagnoses.

The rates of hospitalizations were determined for the five most common specific diagnoses within each of the 15 broad ICD-9 diagnostic categories. Of the 30 740 diagnoses, 1358 (4.4%) were nervous system disorders. This total number of nervous system disorders was equivalent to 0.2% of the 683 479 service members. This means that neurological disorders that were severe enough to warrant hospitalization were rare during the war. The five most common ICD-9 neurological diagnostic categories were: migraine, mononeuritis of the upper limb and mononeuritis multiplex, disorders of the iris and ciliary body, hearing loss and diseases of the conjunctiva. Three of these five diagnoses related to the sense organs (eyes or ears), rather than to the

Table 1. Summary of 11 studies of Gulf War veterans that included findings of neurological examinations. (NCS, nerve conduction studies; EMG, electromyography; ANS function, autonomic nervous system function; QST, quantitative sensory thresholds; QM, quantitative myometry; CTS, carpal tunnel syndrome; UN, ulnar neuropathy; EP, evoked potentials; AV testing, audiovestibular testing; EEG, electroencephalogram; CT scan, computed tomography brain scan; MRI, magnetic resonance imaging of brain.)

senior author(s) location year(s) of article(s)	Gulf war veterans (GWV)	non-deployed veterans (NDV) or other comparison group(S)	results of neurological examinations	results of NCS and/or EMG	other types of neurological testing	neurological diagnoses, if any
Eisen & Kang National Survey in US 2000, 2004, 2005	1061 GWV	1128 NDV	no difference between GWV and NDV on rates of peripheral neuropathy on neuro examinations	no difference between GWV and NDV on rates of peripheral neuropathy on NCS	—	rates of peripheral neuropathy were 4.8% in GWV and 5.9% in NDV
Bourdette & McCauley Oregon and Washington 1999, 2001, 2002	241 ill GWV; 113 healthy GWV	—	no differences on neuro examinations between ill GWV and healthy GWV	some veterans had sensory symptoms that were not confirmed when tested with NCS	—	—
Wessely & Sharief National survey in UK 1999, 2002, 2004	49 ill GWV; 26 healthy GWV	13 ill Bosnia veterans; 22 ill NDV	neuro examinations were unremarkable in four groups of veterans	no evidence of peripheral neuropathy on NCS and EMG in four groups of veterans	ANS function QST QM muscle biopsy muscle metabolism	Among four groups of veterans: eight cases of CTS and three cases of UN
Kelsall & Sim National survey in Australia 2005	1382 GWV	1376 NDV	no differences on neuro examinations between GWV and NDV	—	—	no differences in rates of four categories of disorders between GWV and NDV
Fukuda 193rd Air National Guard in US 1995, 1998	99 ill GWV; 59 healthy GWV	—	no differences on neuro examinations between ill GWV and healthy GWV	—	—	—
Haley 24th Seabees in US 1997, 2000, 2004	23 ill GWV; 10 healthy GWV	10 healthy NDV	no differences on neuro examinations between ill GWV and controls	five ill GWV had NCS and EMG; four had mild abnormalities on NCS; all EMG were normal	ANS function EP AV testing	—
Jamal Glasgow, Scotland 1996	14 ill GWV	13 healthy civilians	no differences on neuro examinations between GWV and controls[a]	no differences on EMG between GWV and controls; no differences on NCS between GWV and controls[a]	EP QST	—
Newmark Seattle, Washington 1995	65 ill GWV	—	58 out of 65 had normal neuro examinations	—	EEG sleep studies	among 65 GWV: 16 GWV were normal, 24 had headaches, 14 had sleep problems, one had CTS, one had UN, nine had other diagnoses

(*Continued.*)

Table 1. (*Continued.*)

senior author(s) location year(s) of article(s)	Gulf war veterans (GWV)	non-deployed veterans (NDV) or other comparison group(S)	results of neurological examinations	results of NCS and/or EMG	other types of neurological testing	neurological diagnoses, if any
Amato San Antonio, Texas 1997	20 ill GWV	—	all neuro examinations were normal, except for two cases of CTS	NCS were normal, except for two cases of CTS; EMG were normal	EEG CT scan muscle biopsy muscle metabolism	two cases of CTS
Rivera-Zayas San Juan, Puerto Rico 2001	12 ill GWV	—	all neuro examinations were normal	all NCS and EMG were normal	—	two cases of CTS
Lee London, UK 2005	33 ill GWV	—	26 out of 33 had normal neuro examinations	—	CT scan or MRI EEG bone scans X-rays of spine	among 33 GWV: 26 were normal, two had CTS, five had other diagnoses

[a] No differences, after adjustment for multiple statistical comparisons.

broader nervous system. Carpal tunnel syndrome is the most common diagnosis in younger populations within the ICD-9 category of mononeuritis of the upper limb and mononeuritis multiplex.

The rates and types of hospitalizations were compared between 652 979 American GWVs and an equal number of non-deployed veterans (Gray *et al.* 2000). A major strength of this study was that it included follow-up of all active-duty and Reserve/National Guard service members for whom demographic data were available (94% of the total of 697 000 GWVs). Data were collected from 1 August 1991 to 31 December 1994 from three hospital systems: DoD hospitals nationwide, Department of Veterans Affairs (VA) hospitals nationwide and all civilian hospitals in the state of California. The total numbers of hospitalizations of GWVs and non-deployed veterans in each system were: 182 164 in the DoD system, 16 030 in the VA system and 5185 in California. The proportions of all hospitalizations that were due to neurological disorders were 3.7% in the DoD system, 4.2% in the VA system and 1.5% in California. In the DoD system, the rates of hospitalization for neurological diseases were the same for GWVs and non-deployed veterans. In the VA and California systems, the rates of hospitalization for neurological diseases were significantly lower in GWVs, compared to non-deployed veterans.

In a more detailed study, 73 218 (13.4%) of 546 522 service members who were on active-duty status during the Gulf War were hospitalized in the DoD hospital system at least once during the period of 1 August 1991–6 June 1994 (Smith *et al.* 2004*b*). Among these hospitalizations, 4229 (5.8%) were for nervous system disorders. The five most frequent ICD-9 neurological diagnostic categories were: mononeuritis of upper limb and mononeuritis multiplex, migraine, mononeuritis of lower limb, strabismus and other disorders of binocular eye movement and other disorders of middle ear and mastoid. Each of these diagnostic categories was present in 0.1% or fewer of the 546 522 veterans. Two of these five diagnoses related to the sense organs (eyes or ears) rather than to the broader nervous system.

(b) *Registry data on neurological disorders*

The Department of Veterans Affairs initiated the Gulf War Registry Health Examination Program (VA Registry) in 1992 to provide medical examinations, laboratory tests and referrals to veterans who had health concerns that they believed were related to the war (VA & DoD 2002). The DoD Comprehensive Clinical Evaluation Program (CCEP) was initiated in 1994 with similar objectives (VA & DoD 2002; Smith *et al.* 2004*b*). At the time that CCEP was initiated, approximately 285 000 GWVs remained on active-duty (Joseph & the Comprehensive Clinical Evaluation Program Evaluation Team 1997). The VA Registry and the CCEP were implemented nationally in all VA and DoD medical facilities, respectively.

As of 1 April 1996, 20 000 GWVs had been evaluated in the CCEP (Joseph & the Comprehensive Clinical Evaluation Program Evaluation Team 1997). Diseases of the nervous system and sense organs (eyes

and ears) constituted 5.8% of the primary diagnoses in these 20 000 veterans. Forty-two individuals (0.2%) were diagnosed with peripheral neuropathy or polyneuropathy. More than 800 individuals, who had neuromuscular symptoms, received neuropsychological evaluations. Three hundred of these 800 veterans received nerve conduction studies (NCS) and electromyography (EMG). No common or distinctive organic pathology was identified among these 800 veterans.

A combined analysis was performed on the clinical findings of 100 339 GWVs who had been evaluated in the VA Gulf War Registry or the CCEP (VA & DoD 2002). This included 32 876 individuals who had been evaluated in the CCEP and 70 385 individuals who had been evaluated in the VA Registry, as of September 1999. Medical evaluations yielded neurological diagnoses relatively rarely. Among the first 49 079 individuals in the VA Gulf War Registry, the most frequent ICD-9 nervous system diagnoses were migraine, hearing loss, tinnitus, carpal tunnel syndrome and myopia. Migraine ('migraine, unspecified' and 'variants of migraine') was diagnosed in 834 individuals (1.7% of the total of 49 079 participants). Carpal tunnel syndrome was diagnosed in 205 individuals (0.4% of 49 079). In the CCEP, the most frequent ICD-9 nervous system diagnoses were migraine, hearing loss, carpal tunnel syndrome, tinnitus and myopia. Migraine (migraine, unspecified and 'common migraine') was diagnosed in 1941 individuals (5.9% of the total of 32 876 participants in the CCEP). Carpal tunnel syndrome was diagnosed in 349 individuals (1.1% of 32 876).

In the UK, the Ministry of Defence initiated the Medical Assessment Programme (MAP) in October 1993 (Bale & Lee 2005). The purpose of the programme was to provide systematic medical evaluations to veterans who believed their health had been affected by service in the Gulf War. From May 1993 to 2004, a total of 3233 GWVs were evaluated in the MAP. A total of 157 veterans (4.9%) were diagnosed with neurological diseases. Migraine, the most frequent central nervous system (CNS) disorder, was diagnosed in 43 veterans (1.3% of 3233). Carpal tunnel syndrome, the most frequent PNS disorder, was diagnosed in 14 veterans (0.4%).

In summary, the overall rates of neurological disorders have been low in veterans who have been admitted to hospitals or who have participated in the Gulf War Registry programs. The rates of hospitalizations for neurological disorders in three hospital systems were the same or significantly lower in GWVs, compared to the rates in non-deployed veterans (Gray *et al.* 2000). Migraine was the most prevalent ICD-9 diagnostic category within the CNS in hospitalization and Registry studies (VA & DoD 2002; Smith *et al.* 2004*b*; Bale & Lee 2005). The rates of PNS disorders were lower than the rates of migraine in most of the hospitalization and Registry studies. The most prevalent ICD-9 diagnostic category within the PNS was mononeuritis of the upper limb and mononeuritis multiplex, which includes carpal tunnel syndrome (VA & DoD 2002; Smith *et al.* 2004*b*; Bale & Lee 2005).

(c) *Population-based epidemiological studies*

In 1995–1998, VA performed the largest population-based survey, entitled the 'National Health Survey of Gulf War Era Veterans and Their Families', which included 20 917 participants (Kang *et al.* 2000). In 1999–2001, a randomly selected subset of these veterans was invited to participate in a 2-day examination at one of 16 VA Medical Centers (Davis *et al.* 2004; Eisen *et al.* 2005). Evaluations included general physical, neurological, gynaecological and psychiatric examinations, standard clinical lab tests, pulmonary function tests, NCS and neuropsychological testing. A total of 1061 GWVs and 1128 non-deployed veterans were examined. The primary health outcomes were chronic fatigue syndrome (CFS), fibromyalgia (FM) and peripheral neuropathy. The prevalence of CFS was significantly increased in the GWVs (rates of 1.6% versus 0.1%), with an adjusted odds ratio (OR) of 40.6. The prevalence of FM was significantly increased in the GWVs (rates of 2.0% versus 1.2%), with an OR of 2.3. The rates of some illnesses were actually higher in the controls than in the GWVs, including peripheral neuropathy (5.9% in controls versus 4.8% in GWVs). This study and its accompanying editorial concluded that: the physical health of deployed and non-deployed veterans was similar; there was no unique syndrome; and similar symptoms had been reported after previous conflicts (Eisen *et al.* 2005; Komaroff 2005).

5. DO THE NEUROLOGICAL TYPE SYMPTOMS CLUSTER IN A WAY THAT MIGHT SUGGEST SPECIFIC NEUROLOGICAL DISORDERS?

In neurological practice, the combination of symptoms, signs and laboratory investigations may clearly point to a specific neurological diagnosis. This is clearly the case with the registry and hospitalization data that documented specific neurological diagnoses, as described above. It is also the case with those diagnosed with disorders such as ALS (motor neuron disease), as described below. However, there was early speculation that illnesses in some GWVs might represent a new neurological disease (or a range of diseases) that was previously unrecognized.

The Portland Environmental Hazards Research Center performed a population-based case–control study, which was designed to compare GWVs who reported unexplained symptoms that could not be diagnosed with healthy GWVs (McCauley *et al.* 1999; Bourdette *et al.* 2001; McCauley *et al.* 2002). Cases and controls were selected from respondents to a survey, which was mailed in 1995–1997 to a representative sample of 2022 GWVs who lived in Oregon and Washington. Questions focused on chronic fatigue, psychological and cognitive symptoms and musculoskeletal symptoms. A total of 443 potential cases of unexplained illnesses and healthy controls were recruited for clinical evaluations. The evaluations included a physical examination with an emphasis on neurological and musculoskeletal systems, a detailed health history, psychological and neurobehavioural tests and NCS (if indicated). Potential cases were excluded from the study if they were diagnosed with several medical conditions; the

most frequent exclusions were for diabetes, hepatitis B or C, cancer and HIV infection. The 241 GWVs who had unexplained symptoms that were not attributable to a medical diagnosis after a thorough clinical evaluation were compared with 113 healthy GWVs (Bourdette *et al.* 2001). Among the 241 cases, 87% had unexplained cognitive symptoms, 38% had unexplained musculoskeletal symptoms and 42% had unexplained fatigue. Few clinical differences were found between cases and controls; and 'no unequivocal findings' were determined on physical examinations or neurological examinations. There was no clustering of neurological findings that convincingly supported a single clinical syndrome.

A population-based survey was mailed in 1997–1998 to three randomly selected samples of British veterans including 3531 GWVs, 2058 veterans of the 1992–1997 Bosnia conflict and 2614 veterans who did not deploy outside of Great Britain (Ismail *et al.* 1999; Unwin *et al.* 1999). Deployed personnel reported a higher prevalence of symptoms than the two comparison groups, but the patterns of symptoms did not differ between the groups. The findings did not support a syndrome that was unique to GWVs.

In 1994–1995, Haley and colleagues surveyed 249 members of 606 GWVs (41%) who were part of the 24th Naval Mobile Construction Battalion ('Seabees') (Haley *et al.* 1997*b*). This reserve battalion was located in five southeastern states. In 1992, members of this unit reported a high prevalence of symptoms to Navy physicians (Institute of Medicine 1995; IOM 1996). Therefore, the 24th Seabees were investigated because they were 'known to have a high prevalence of postwar illness' (Haley *et al.* 1997*b*). There was no comparison group. The veterans completed questionnaires that included hundreds of symptoms. There were 22 major symptoms, e.g. tingling or numbness. Each major symptom had four to 20 sub-questions, e.g. there were 13 discrete anatomical locations for tingling or numbness.

The authors performed a two-stage statistical analysis (factor analysis) to determine patterns of symptoms that clustered together. Six different clusters of symptoms were identified. Each cluster was defined by symptoms that correlated with each other. The authors hypothesized that these symptoms that correlated with each other ('syndromes') were 'variants of generalized injury to the nervous system'. The authors focused detailed investigations on individuals who reported symptoms in three of the six clusters, which were defined as follows:

(i) 'Syndrome 1: impaired cognition' (total of 12 cases, out of 249 in survey); symptoms included distractibility, difficulty remembering, depression, insomnia, excessive daytime sleepiness, slurring of speech, confused thought process and migraine-like headaches.
(ii) 'Syndrome 2: confusion-ataxia' (total of 21 cases, out of 249 in survey); symptoms included problems with thinking processes, such as reading, writing and spelling; getting confused, not knowing where they are or what they are doing; problems with keeping their balance, stumbling often and feeling like the room is spinning; having a physician's diagnosis of PTSD, depression or liver disease; and sexual impotence.
(iii) 'Syndrome 3: arthro-myo-neuropathy' (total of 22 cases, out of 249 in survey); symptoms included generalized joint and muscle pains; increased difficulty lifting heavy objects; muscle exhaustion after exertion; and tingling or numbness of the hands, arms, feet and legs.

All the three of these proposed syndromes could have a neurological basis, but it is also possible that they could have a psychiatric or neuropsychological basis. These 'syndromes' were based solely on a statistical analysis of symptoms. Neurological examinations and neurophysiology tests were required to determine if they truly represented neurological disorders, as described below.

The symptoms of 65 GWVs who were on active-duty in the Seattle area and Alaska and who were evaluated in the CCEP were analysed to look for evidence of unusual clusters of patients with similar diagnoses and for evidence of any new neurological syndromes (Newmark & Clayton 1995). Fifty-eight of the 65 patients (89%) had normal neurological examinations. Forty-two of these 58 had reported at least one neurological symptom. The other seven individuals had one or more abnormalities. Each of these abnormalities was unique and no abnormal examinations were similar. The conclusion was that no consistent patterns of neurologic disease or new neurologic syndromes had emerged.

6. ARE THE NEUROLOGICAL SYMPTOMS REPORTED BY GWVS ASSOCIATED WITH ANY OBJECTIVE NEUROLOGICAL ABNORMALITY; AND IF SO, DO THESE NEUROLOGICAL ABNORMALITIES SUGGEST ANY PATTERN OF KNOWN NEUROLOGICAL DISEASE OR SPECIFIC NEUROLOGICAL SYSTEM IMPAIRMENT?

(a) *Overview and findings of neurological examinations*

Most studies have included comprehensive assessments with neurological examinations and laboratory investigations, while others have focused on testing for specific types of neurological dysfunction, such as peripheral neuropathy or autonomic nervous system dysfunction. The majority of studies have concentrated on the most symptomatic cases, either self-selected or investigator-selected on the basis of symptoms. To address the question of objective abnormalities, the findings of neurological examinations are presented first, followed by the findings of various types of specialized testing. The findings of neurological examinations in nine studies are reviewed, including four population-based studies, two cluster investigations and three small clinical studies.

Peripheral neuropathy was a major focus of the VA National Health Survey, which included 1061 GWVs and 1128 non-deployed veterans (Davis *et al.* 2004; Eisen *et al.* 2005). Distal symmetric peripheral neuropathy (DSP) was defined as distal sensory, motor or

sensorimotor polyneuropathy, that was identified on the basis of abnormalities on standardized neurological examination, standardized NCS or both. There were no differences between the GWVs and non-deployed veterans in the rates of DSP diagnosed by neurological examination alone, NCS alone, or by a combination of both. Based on the combination of neurological examination and NCS, DSP was diagnosed in 6.3% of the GWVs and 7.3% of the non-deployed veterans. The three types of DSP were stratified into sensory only, motor only and sensorimotor. There were no differences in the rates of each type between the GWVs and non-deployed veterans. Twenty-three GWVs and 21 non-deployed veterans had a medical condition that could have caused the neuropathy. These conditions included abnormalities of upper motor neuron function, which implied CNS disease and several diseases, including alcohol dependence, diabetes and hypothyroidism. After these individuals were removed from the analysis, the rates of DSP were 4.8% in the GWVs and 5.9% in the non-deployed veterans. The conclusion was that there was no evidence that deployment to the Gulf War caused chronic peripheral nerve damage that was present 10 years later.

As detailed above, 241 ill GWVs were compared with 113 healthy GWVs in the Portland, Oregon study (Bourdette *et al.* 2001). There were no differences found on neurological examinations between ill and healthy veterans.

A sub-group of the UK study (Unwin *et al.* 1999) was investigated to determine if the neuromuscular symptoms reported by some GWVs were related to objective abnormalities of peripheral nerves, skeletal muscles or neuromuscular junctions (Sharief *et al.* 2002; Rose *et al.* 2004). Symptomatic veterans were randomly selected from the original three groups (deployed to the Gulf War, deployed to Bosnia and not deployed) on the basis of five or more neuromuscular symptoms. These included fatigue, joint stiffness, muscle weakness, myalgia at rest or after exercise, sensory symptoms (e.g. numbness of the fingers or toes) and autonomic symptoms (e.g. disturbances of bladder, bowel or sexual function). Healthy GWVs were randomly selected from those who reported zero or one of these neuromuscular symptoms. Comprehensive evaluations were performed, including neurological examinations; NCS; quantitative sensory thresholds (thermal and vibration); autonomic function tests (cardiovascular reflexes and sympathetic skin response); and concentric needle and single-fibre EMG.

One hundred and ten veterans participated in the British study, including 49 ill GWVs, 26 healthy GWVs, 13 ill veterans of peace enforcement missions in Former Yugoslavia and 22 ill non-deployed veterans (Sharief *et al.* 2002; Rose *et al.* 2004). Neurological examinations were generally unremarkable; and there was no clinical evidence for peripheral neuropathy or fatigable muscle weakness. Quantitative myometry was also employed to assess muscle strength and fatigue more rigorously. Service members who were still on active-duty were objectively stronger than those who had been discharged from service. However, quantitative strength and muscle fatigue testing did not correlate with self-reported symptoms or fatigue in any of the four groups of veterans. There were significant associations between some of the qualitative strength tests and self-reported symptoms of weakness; however, none of these associations were related specifically to Gulf War service. The results of the special investigations are described below.

The population-based study of GWVs and non-deployed veterans in Australia compared rates of neurological symptoms and the findings of neurological examinations (Kelsall *et al.* 2005). This study included 1382 (74%) of the total of 1871 service members who deployed to the Gulf War. Most Australian GWVs were naval personnel who deployed to the war on frigates, destroyers or supply ships. The comparison group included 1376 Australian service members who did not deploy. This study, which was conducted in 2000–2002, used a questionnaire that included 17 neurological symptoms. GWVs reported higher rates of nearly all of these neurological symptoms, compared to non-deployed veterans. Several outcomes were compared between the two groups, which were defined on the basis of a combination of neurological symptoms and abnormalities on examination. The outcomes included possible myopathy, possible disorder of the anterior horn cells, possible CNS disorder and epilepsy. Disorders of the anterior horn cells were of particular interest because of the possible increase in the incidence of ALS in GWVs in the US (see below). In addition, a Neuropathy Score was calculated, which was based solely on abnormalities on examination of the cranial nerves, muscle strength, muscle reflexes and sensory function in the extremities. There was no difference between the two groups on the rates of objective abnormalities on neurological examination and the Neuropathy Score was the same in both groups of veterans. Possible anterior horn cell disease was found in 1.5% of the GWVs, compared to 2.0% of the controls. Similarly, there were no significant differences between the two groups in the rates of possible myopathy, possible CNS disorder or possible epilepsy. The conclusion was that there was no evidence of an increase in objective neurological abnormalities in GWVs.

The CDC study included medical histories, structured psychiatric interviews, physical examinations and clinical lab tests in 158 of the 490 deployed members of the Pennsylvania 193rd Air Force National Guard unit. This unit was chosen for evaluation because a physician at a nearby VA Medical Center reported a high prevalence of illness (Centers for Disease Control and Prevention (CDC) 1995; IOM 1996). The CDC developed a working case definition that required at least two symptoms of fatigue, musculoskeletal pain and/or problems with mood or cognition for at least six months (Fukuda *et al.* 1998). Of the 158 unit members, 8% complained of two or more severe symptoms. Fifty-four per cent complained of two or more mild-to-moderate symptoms and 37% reported one or no symptoms (controls). Physical examinations were most notable for the general paucity of abnormal findings. Several minor abnormalities were found on neurologic examination, but no abnormalities were associated with cases. In contrast, the prevalence of current psychiatric illness was much higher in the cases than

in the controls, including major depression (in 18 cases and one control), somatization disorder (in four cases), panic disorder (in three cases) and PTSD (in one case).

Haley and colleagues identified the 23 Seabees who reported the most symptoms and invited them to participate in exhaustive medical evaluations (Haley *et al.* 1997*a*). These included five of the 12 individuals with Syndrome 1, 13 of the 21 individuals with Syndrome 2 and five of the 22 individuals with Syndrome 3. These 23 individuals represented only 4% of the 606 GWVs in the 24th Seabees. Two groups of healthy controls were used: ten GWVs from the 24th Seabees and ten veterans selected from the 150 members of the 24th Seabees who did not deploy. In 1995, the mean age of the 23 cases was 47 years, compared to a mean age of 31 years for all US GWVs. One hundred sixty-five (165) neurological measurements were performed. There was no correction made for multiple statistical tests. The results of the special investigations are described below.

As part of this comprehensive evaluation, six neurologists reviewed the clinical findings for each of the 23 ill veterans and 20 healthy veterans to attempt to arrive at a consensus diagnosis (Haley *et al.* 1997*a*). These neurologists had not participated in the examinations of these 43 subjects and they conducted their review blinded to case–control status. The neurologists concluded that the clinical and laboratory findings were non-specific and not sufficient to diagnose any known neurological syndrome. Detailed neurological examinations demonstrated that about two-thirds of the 43 subjects had one or more neurological abnormalities (most frequently, reduced strength in the lower extremities). The proportion of subjects with abnormalities on neurological examination was the same in the 23 ill veterans and the 20 controls. This absence of significant differences in the neurological examinations of the cases and controls does not support the authors' interpretation of neurological injury in the 23 cases.

Twenty-two ill veterans and 18 healthy controls studied in 1994–1995 were re-evaluated in 1997–1998 (Haley *et al.* 2000). The objective of the follow-up study was to perform neuroimaging. Neurological examinations were repeated during the re-evaluation and the findings were still unremarkable.

In contrast to the results of the neurological examinations, the rates of medical diagnoses and psychiatric diagnoses were substantially higher in the ill veterans than in the healthy controls. Ten of 21 of the ill veterans had medical diagnoses, compared to four of 17 of the controls (Haley *et al.* 2004). Thirteen of 21 of the ill veterans (62%) were diagnosed with major depressive disorder, compared to two of 17 of the controls (12%). Three of 21 of the ill veterans were diagnosed with PTSD, compared to none of the controls.

Twenty GWVs, who had participated in the CCEP, were selected because they reported severe symptoms of muscle fatigue, weakness or myalgias that interfered with their daily activities for at least six months (Amato *et al.* 1997). They underwent an extensive neuromuscular evaluation at Wilford Hall Medical Center in San Antonio, Texas, which included neurological examinations, manual muscle strength testing of 36 muscle groups, exercise forearm tests, electroencephalography (EEG), NCS of the upper and lower extremities, repetitive nerve stimulation quantitative and single fibre EMG, several blood tests and muscle biopsies. The neurological examinations, including muscle strength testing, were within normal limits, except for two patients with probable carpal tunnel syndrome. The results of several blood tests were unremarkable, except for a mild increase in creatine kinase levels in six patients. No connective tissue diseases or infectious diseases were diagnosed. The results of the special investigations are described below. Despite severe subjective symptoms, most of the patients had no objective evidence of neuromuscular disease; and there was no evidence of specific neuromuscular disorder in any patient. Psychiatric evaluations of these patients revealed depression or anxiety disorders in ten patients, somatoform disorders in three patients and a conversion disorder in one patient.

Veterans who had previously been evaluated in the VA Gulf War Registry were mailed a survey that focused on symptoms of peripheral neuropathy (Rivera-Zayas *et al.* 2001). Twelve of these veterans, who reported constant numbness, paraesthesias and cramps in the extremities, were selected for detailed evaluations at the San Juan, Puerto Rico VA Medical Center. Neurological examinations, including muscle stretch reflexes, manual muscle testing and sensory evaluation of limbs, were normal in all cases. Neurophysiology was also normal, as described below.

Among the first 1000 veterans who participated in the UK Medical Assessment Programme, 33 veterans reported possible neurological symptoms, e.g. tingling paraesthesias, muscle twitches or muscle weakness (Lee *et al.* 2005). These veterans were referred to neurology experts in London. Evaluations included magnetic resonance imaging (MRI) or computed tomography (CT) brain scans, NCS and EMG. Some veterans had EEG, bone scans and cervical or lumbar spine X-rays. Twenty-six individuals had no evidence of a neurological disorder. Two individuals had multiple sclerosis that had been diagnosed previous to participation in the MAP. One individual was diagnosed with mixed motor-sensory peripheral neuropathy, two individuals were diagnosed with essential tremors and two individuals were diagnosed with carpal tunnel syndrome.

(b) *Specific neurological investigations*

(i) *Neurophysiology*

The findings of NCS and EMG in 10 studies are reviewed, including three population-based studies, one cluster investigation, two controlled clinical studies and four small clinical studies.

As detailed above, the rates of peripheral neuropathy in the VA National Health Survey were lower in GWVs (4.8%), than in non-deployed veterans (5.9%; Davis *et al.* 2004; Eisen *et al.* 2005). Some of the 241 ill GWVs in the population-based study in Portland, Oregon reported symptoms of mild distal sensory impairment; however, these subjective symptoms were not confirmed when evaluated on NCS (Bourdette *et al.* 2001).

In the British population-based study of 110 veterans, NCS ruled out axonal or demyelinating peripheral neuropathy (Sharief *et al.* 2002). Eight individuals were diagnosed with mild median nerve compression (carpal tunnel syndrome), including two ill GWVs, two healthy GWVs, one ill Bosnia veteran and three ill non-deployed veterans. Three individuals were diagnosed with mild ulnar neuropathy, including one ill GWV and two ill non-deployed veterans. Detailed EMG testing was performed to rule out chronic denervation, myopathic changes and abnormalities of neuromuscular transmission, and there were no significant differences found among the four groups of veterans.

In the study of the 24th Seabees, NCS and EMG were performed in the upper and lower extremities of three of the Syndrome 2 cases and two of the Syndrome 3 cases (Haley *et al.* 1997*a*). There were a few borderline abnormalities in the NCS in four of the five cases. The EMG tests were within normal limits in all five cases.

One of the earliest neurophysiology studies, which was conducted in Glasgow, Scotland, compared 14 ill GWVs with 13 healthy civilians from the general population (Jamal *et al.* 1996). The ill veterans were recruited from a veterans' advocacy organization, since they complained of an 'unexplained illness' after the Gulf War. Symptoms in the ill veterans included fatigability, weakness, paraesthesias, numbness and pain. Assessment included detailed neurological examinations; three quantitative measures of sensory function (heat, cold and vibration); 12 measures of motor and sensory nerve conduction in the upper and lower limbs; seven measures of evoked potentials (visual, brainstem auditory and somatosensory) and needle EMG of the distal and proximal muscles. There were no differences between the ill veterans and controls in the evoked potentials or the needle EMG. After adjustment for multiple statistical comparisons, there were no differences in the NCS and the only statistical difference between the groups was in the quantitative sensory testing for cold threshold. The authors did not diagnose peripheral neuropathy in any subject.

Fifty-six GWVs who had neuromuscular symptoms were referred to the physical medicine and rehabilitation electrodiagnostic laboratory at Walter Reed Army Medical Center (Joseph *et al.* 2004). The most frequent symptoms were numbness in the upper or lower extremity, lower back pain, lower extremity pain and neck pain. For a comparison group, medical records were retrieved for 120 non-deployed adults who had similar symptoms and who were evaluated during the same period. The evaluation included motor and sensory conduction studies and needle EMG of upper and lower extremities, depending on the clinical symptoms. Rates of three health outcomes were compared: radiculopathy of the upper or lower extremities, generalized peripheral polyneuropathy and compression neuropathy (such as carpal tunnel syndrome). One GWV was diagnosed with radiculopathy (2% of 56 veterans), compared with 19 controls (16% of 120 individuals), which was a significant difference. Four per cent of GWVs were diagnosed with peripheral polyneuropathy, compared with 5% of controls. Thirteen per cent of GWVs were diagnosed with compression neuropathy, compared with 27% of controls. A second analysis was performed that included only the individuals who were male and on active-duty status (41 GWVs and 47 non-deployed veterans). The findings were similar in these smaller groups. Thus, there was no objective evidence of an increased incidence of neuromuscular disorders in symptomatic GWVs, compared with symptomatic controls. Indeed, there was a lower incidence of positive electrodiagnostic testing in the GWV group, suggesting a lower threshold for referral of Gulf War patients than for non-Gulf War patients.

Among 65 GWVs evaluated in the CCEP in Seattle, the authors classified the neurological diagnoses of the patients into four categories: normal (16 patients), headache (24), sleep problem (14) and other (11; Newmark & Clayton 1995). Among the 11 patients with 11 different neurological diagnoses, there were two patients with neuropathies (one had unilateral carpal tunnel syndrome and one had unilateral, post-traumatic ulnar neuropathy).

In the Texas study of 20 ill GWVs, the NCS were normal, except for two patients with carpal tunnel syndrome (Amato *et al.* 1997). The quantitative EMG were normal in all patients. The single fibre EMG was normal, except for a mild abnormality in one patient. There was no evidence of axonal or demyelinating polyneuropathy, or abnormalities of the neuromuscular junction.

In the Puerto Rican study, motor and sensory NCS and needle EMG were performed in the upper and lower extremities (Rivera-Zayas *et al.* 2001). There was no evidence of axonal or demyelinating polyneuropathy in any of the 12 patients on NCS. Also, there were no EMG abnormalities in any patient. Indeed, all of the testing was within normal limits, except for two veterans who were diagnosed with bilateral carpal tunnel syndrome. Both veterans had occupations that required repetitive activities of the arms, a known risk factor for carpal tunnel syndrome.

Among the first 1000 veterans who participated in the UK Medical Assessment Programme, 33 veterans reported possible neurological symptoms and all 33 were evaluated with NCS and EMG (Lee *et al.* 2005). One veteran was diagnosed with mixed motor-sensory peripheral neuropathy and two veterans were diagnosed with carpal tunnel syndrome.

Altogether, there have been four studies that systematically utilized neurological examinations, NCS and EMG to diagnose GWVs who had neuromuscular symptoms (Amato *et al.* 1997; Rivera-Zayas *et al.* 2001; Sharief *et al.* 2002; Lee *et al.* 2005). In addition, NCS and/or EMG were also applied to subgroups of other studies, as detailed above. The great majority of NCS and EMG studies were within normal limits. The only consistent finding was that a small proportion of veterans were diagnosed with compression neuropathies (carpal tunnel syndrome or ulnar neuropathy).

(ii) *Autonomic function*

Four studies have evaluated autonomic nervous system function in GWVs. The British study of 110

veterans evaluated autonomic function, specifically cardiovascular reflexes and sympathetic skin response. There were no significant differences of autonomic function among the four groups of veterans (Sharief *et al*. 2002).

Twenty-one of the 23 ill veterans and 17 of the 20 healthy controls in the Seabees study participated in a comprehensive study of autonomic nervous system function (Haley *et al*. 2004). Circadian rhythm of heart rate variability was measured by 24 h electrocardiography (Holter monitoring). High-frequency heart rate variability increased normally during sleep in the controls, but not in the ill veterans. The mean heart rate of ill veterans also declined less at night, compared to the controls. Both of these measurements were significantly different between ill veterans and controls. The authors interpreted this to mean an abnormality of the neuroregulation of high-frequency heart rate variability, indicating a subtle abnormality of parasympathetic nervous system activity. However, the authors stated that they could not attribute the specific symptoms of the ill veterans 'directly to early autonomic dysfunction'. Other testing included ambulatory blood pressure recording, Valsalva ratio testing, poly-somnography, sympathetic skin response evaluation and sweat imprint testing (the latter two tests measure sympathetic function). There were no significant differences between the ill veterans and controls on several measures of sympathetic adrenergic function, the skin and sweat tests, sleep architecture, respiratory function and circadian variation in blood pressure and temperature. The authors concluded that the findings indicated normal sympathetic nervous system function.

Autonomic nervous system control of cardiovascular function was evaluated in GWVs who were diagnosed with CFS and in healthy GWVs at the East Orange, New Jersey VA Medical Center (Peckerman *et al*. 2000, 2003). The objective of these studies was to compare cardiovascular responses to a variety of stressors in three groups of GWVs: 16 veterans who had CFS and PTSD, 39 veterans with CFS only and 47 healthy veterans. These two studies evaluated if altered control of cardiovascular responses during stress could be part of the underlying mechanism of fatigue in some GWVs with CFS. PTSD can also cause significant changes in autonomic function and could possibly alter cardiovascular responses. In comparison to the healthy veterans, the 16 veterans with CFS and PTSD demonstrated abnormal responses in cardiovascular regulation. The 39 ill veterans with CFS only did not demonstrate abnormal responses. The 16 veterans with CFS and PTSD demonstrated a significantly reduced ability to regulate blood pressure, whether it was in response to a mental effort that called for an increase in blood pressure, or in response to the normal reflex response of recovery of blood pressure after standing up. The authors concluded: 'Comorbid PTSD contributes to dysregulation of cardiovascular responses to mental and postural stressors in Gulf veterans with medically unexplained fatiguing illness and may provide a physiological basis for increased somatic complaints in Gulf veterans with symptoms of posttraumatic stress'.

Autonomic nervous system function was evaluated in FM patients, ill GWV and healthy controls (Stein *et al*. 2004). Abnormalities of autonomic function have been found in previous studies of female FM patients, based on the analysis of heart rate variability. This study included 18 healthy males and 18 healthy females who were recruited from the community, seven male FM patients, 19 female FM patients, six male GWV and five female GWV. GWV were eligible to participate if they reported at least two of three symptoms: fatigue that limited usual activity, musculoskeletal pain and cognitive symptoms including memory, concentration or attention difficulties. Heart rate variability was measured with 24 h Holter monitoring performed at Georgetown University. Heart rate indices were calculated related to 11 time and frequency domains. Heart rate variability indices were similar in healthy men and women. Women who had FM or who were GWV demonstrated significantly lower heart rate variability, compared to men who had FM or who were GWV. A different pattern emerged when FM patients of one gender, or GWV of one gender, were compared to healthy controls of the same gender. Male FM patients or male GWV demonstrated no differences in heart rate variability, compared to healthy male controls. Female FM patients or female GWV demonstrated significantly decreased heart rate variability, compared to healthy female controls. The authors concluded that decreased heart rate variability in FM and GWV appeared to be gender dependent; however, they stated that the mechanisms that were responsible for this abnormality were unknown. The authors did not adjust the heart rate variability indices for depression symptoms, even though previous studies have demonstrated that depression is associated with abnormalities of heart rate variability (van de Borne 2004).

Four studies evaluated autonomic nervous system function in GWVs. Each study investigated the regulation of cardiovascular function, which yielded conflicting results (Peckerman *et al*. 2000, 2003; Sharief *et al*. 2002; Haley *et al*. 2004; Stein *et al*. 2004). Only one of the four studies was population-based, and it demonstrated no differences in cardiovascular regulation between GWVs and controls (Sharief *et al*. 2002). Two of the four studies also evaluated another type of autonomic nervous system function, i.e. sympathetic skin response (Sharief *et al*. 2002; Haley *et al*. 2004). Both studies demonstrated no difference on this response between GWVs and controls.

(iii) *EEG*

During the early implementation of the CCEP in 1994, neurological referrals and EEG were mandatory for all CCEP patients, regardless of symptoms (Newmark & Clayton 1995). Forty-seven of the 65 patients in the Seattle study underwent EEG, of which 43 were within normal limits. Four individuals had EEG with unique abnormalities. The authors classified the neurological diagnoses of the 65 patients into four categories: normal (16 patients), headache (24), sleep problem (14) and other (11). Among the 24 patients with headache, about half were migraines and about half

were tension headaches. Among the 14 patients with sleep problems, six had abnormal sleep studies, such as sleep apnoea. This led the authors to suggest that sleep disorders might be under-diagnosed in active-duty populations.

The 20 ill GWVs in the Texas study had normal EEGs (Amato *et al.* 1997). Thirteen of these veterans, who reported headaches, memory loss or difficulty in concentration, had CT brain scans, all of which were normal.

(iv) *Evoked potentials*

In the Glasgow study, seven measures of evoked potentials (visual, brainstem auditory and somatosensory) was compared between 14 ill GWVs and 13 healthy controls (Jamal *et al.* 1996). No differences were found on the evoked potentials between the two groups.

In the study of the 24th Seabees, somatosensory, brainstem auditory and visual evoked potentials were measured (Haley *et al.* 1997*a*). On testing of somatosensory evoked potentials, the proportion of veterans who had one or more abnormalities was the same in the 23 ill veterans and 20 controls (19% of the total of 43 veterans). On testing of brainstem auditory evoked potentials, the proportion of veterans who had one or more abnormalities was the same in the ill veterans and controls (66% of the total of 41 veterans). The abnormalities found in the somatosensory testing and brainstem auditory testing was significantly related to increasing age. The 13 Syndrome 2 cases performed significantly worse on somatosensory function and brainstem auditory function, compared to the controls. The five Syndrome 1 cases performed significantly worse on brainstem auditory function, compared to the controls. There were no differences in any of the parameters of the visual evoked potentials between the ill veterans and controls.

(v) *Audiovestibular testing*

Symptoms of balance problems or vertigo are sometimes caused by abnormalities of audiovestibular function; therefore, the study of the 24th Seabees included several measurements of the audiovestibular system (Haley *et al.* 1997*a*; Roland *et al.* 2000). The definition of Syndrome 2 included symptoms of balance problems and vertigo ('problems keeping their balance and feeling like the room is spinning'), but the definitions of Syndromes 1 and 3 did not. There were significant abnormalities on various audiovestibular measures in the ill veterans who had each of the three syndromes, compared to the controls. The authors of the Seabees study concluded that the 23 ill veterans demonstrated neurological injury. This conclusion was based heavily on the results of the evoked potentials and the audiovestibular testing.

(vi) *Muscle biopsy*

Thirty-four muscle biopsies were performed as part of the British study of 110 veterans (Rose *et al.* 2004). Eighteen biopsies were normal, and 16 biopsies showed a variety of abnormalities. Most of these abnormalities would be considered minor and of doubtful or uncertain significance within the normal clinical setting. None of the particular abnormalities were associated with any of the four groups of veterans. Also, there was no association between abnormalities on the muscle biopsies and the self-reported symptoms of weakness.

Muscle biopsies were normal in 15 of the 20 ill GWVs participating in the Texas study. Five patients had minor, non-specific histological abnormalities, three of which also had mild increases in creatine kinase levels (Amato *et al.* 1997).

(vii) *Muscle metabolism*

Amato *et al.* (1997) and Rose *et al.* (2004) utilized ischaemic forearm exercise testing designed to detect any defects of muscle glycolysis, and no abnormal results were found. There was also no defect of adenylate deaminase activity during the forearm ischaemic test (Rose *et al.* 2004). Additional metabolic problems such as glycogen or lipid storage or mitochondrial disorders were screened by histocytochemical stains of the muscle biopsies, none of which were significantly abnormal (Amato *et al.* 1997; Rose *et al.* 2004). The group of ill GWVs in the British study found an aerobic bicycle exercise test more effortful, and they generated significantly higher plasma lactate concentrations, compared with healthy GWVs (Rose *et al.* 2004). It was not possible to determine if this was due to lack of aerobic fitness, perhaps due to inactivity secondary to ill health; or alternatively, due to subtle mitochondrial damage sustained during Gulf War service.

7. IS THERE EVIDENCE FOR AN INCREASED INCIDENCE OF ANY NEUROLOGICAL DISEASE IN GWVS?

The review thus far has not suggested an increased incidence of any specific neurological disease following Gulf War service. However, there was concern in 1999, when cases of ALS were reported in young servicemen in an age group in which ALS is usually rare. ALS is a rare progressive degenerative disease of unknown aetiology that is generally fatal within 5 years of diagnosis. Accordingly, formal studies to investigate a possible link were launched.

Horner *et al.* (2003) used several active and passive ascertainment methods nationwide, to follow-up the entire population of military personnel who were on active-duty in 1990. This study used DoD and VA databases on inpatient hospitalizations, outpatient visits, prescription drugs and disability compensation was searched to identify possible ALS cases. Over the 10 years from August 1990 to July 2000, 107 cases of ALS were identified and medically confirmed among approximately 2.5 million veterans. Forty ALS cases were diagnosed among 696 118 GWVs and 67 cases were diagnosed among 1 786 215 non-deployed veterans. The risk of ALS was significantly increased among GWVs compared to the controls, with a relative risk of 1.92. In addition, the risks were significantly elevated among GWVs who were in the Air Force or in the Army, compared to their non-deployed counterparts (relative risks of 2.68 and 2.04, respectively). Two GWVs and four non-deployed

veterans had a family history of ALS. The relative risks were similar when the individuals who had a family history were removed from the analysis. This study included detailed interviews to obtain medical, military and environmental exposure histories. These data are being analysed to determine if specific factors can be identified in GWVs that are associated with an elevated risk of ALS.

Haley (2003) performed a study to determine the incidence of ALS in GWVs who were diagnosed before age 45. This study focused on a subset of the GWVs who were included in the study by Horner *et al.* The incidence rate of ALS in GWVs was compared with the rate in the same age group in the general US population. In 1991–1998, 17 cases of ALS were identified and medically confirmed among GWVs who were diagnosed before age 45. The author commented that this number probably reflected an undercount, because of incomplete methods of ascertainment. From 1991 to 1994, four young GWVs were diagnosed with ALS, which is 0.94 times that expected in the general population. From 1995 to 1998, 13 young GWVs were diagnosed with ALS, which is 2.27 times that expected in the general population, which was statistically significant. Haley commented that his findings raised the question if the recent increase in ALS incidence was limited to the GWV population or if it was part of a wider problem in the overall military or civilian populations.

An editorial accompanied the two ALS studies (Rose 2003). It highlighted some methodological limitations of the two studies and cautioned against uncritical acceptance of the small excess risk which it felt was not convincing, especially given the small number of ALS cases and the inherent difficulties regarding differential case ascertainment in the Gulf War population versus the control populations. Furthermore, to date, there has been no evidence of increased mortality from ALS in GWVs in the mortality studies of GWVs in the US and UK.

The relationship between general military service and mortality from ALS was recently evaluated in 408 288 men who were participants in a national study of the American Cancer Society (Weisskopf *et al.* 2005). Enrolment of participants started in 1982, and the median age of men at enrolment was 57 years. Thirty-one per cent of the cohort had served in the military before 1982 and 69% had not been in the military. Causes of mortality were determined for the period of 1989–1998, which identified a total 280 deaths due to ALS. Men who had military service had a significantly increased death rate from ALS, compared to the controls (relative risk of 1.53). This increase in ALS mortality was observed in veterans of the Army, Navy and Air Force. The ALS risk was increased in military veterans from every 5-year birth cohort from 1915 to 1939. The increased risk appeared to be independent of the branch of service, the years when the service occurred, and the number of years of service. These findings were independent of service during the Gulf War, because the military service considered in this study only included the period before 1982. This large study raised the question of whether military service, in general, might increase the risk of ALS, regardless of specific deployments.

8. CONCLUSIONS

Population-based studies are the only type of study that can be extrapolated to the overall Gulf War populations of 697 000 US veterans and 53 000 UK veterans. Overall, the results of the four large population-based epidemiological studies were consistent (Bourdette *et al.* 2001; Sharief *et al.* 2002; Davis *et al.* 2004; Rose *et al.* 2004; Eisen *et al.* 2005; Kelsall *et al.* 2005). These included representative samples from the populations of GWVs from the entire US, from the states of Oregon and Washington, and from the entire UK. The Australian study included the entire population of 1871 Australian GWVs. Each of these studies compared the findings of neurological examinations of GWVs and military controls; and no differences were found in the rates of abnormalities on neurological examination between GWVs and controls. Two of these studies also utilized NCS in all subjects; and there were no differences in the results between GWVs and controls (Sharief *et al.* 2002; Davis *et al.* 2004; Eisen *et al.* 2005).

In addition to these four large epidemiological studies, neurological function in GWVs was evaluated in three large hospitalization studies, as well as 13 smaller studies. In nearly all of the studies, neurological function was normal in most GWVs, except for a small proportion who were diagnosed with compression neuropathies (carpal tunnel syndrome or ulnar neuropathy). In the great majority of controlled studies, there were no differences in the rates of neurological abnormalities in GWVs and controls.

In a national US study, the incidence rate of ALS was significantly increased in GWVs, compared to the rate in non-deployed veterans (Horner *et al.* 2003). However, it is possible that military service, in general, might be associated with an increased risk of ALS, rather than Gulf War service, in particular (Weisskopf *et al.* 2005). VA initiated a National ALS Registry in 2002 to improve its capability to perform research on the causes and treatment of ALS (Kasarkis *et al.* 2004).

Taken together, the findings in the 22 epidemiological and clinical studies lead to the inference that if a neurological examination in a GWV is within normal limits, then extensive neurological testing is unlikely to diagnose occult neurological disorders. This should provide useful guidance to physicians who are providing medical care for GWVs in the US, UK and Australia. Undoubtedly, some GWVs have experienced disabling symptoms that could be related to the CNS or PNS. However, nearly all of the studies have demonstrated few or no underlying neurological aetiologies for these symptoms, with the exception of a small proportion of cases of compression neuropathies.

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